47. (New) The method of claim 46, wherein said vector is an adenoviral vector, adeno-associated viral vector or retroviral vector.

48. (New) The method of claim 42, wherein said estrogen receptor-containing cells are estrogen-dependent tumor cells.

49. (New) The method of claim 48, wherein said estrogen-dependent tumor cells are estrogen-dependent breast cancer cells.

50. (New) The method of claim 42, wherein an antiestrogen compound is further administered to said cells.

REMARKS

I. Nationalization

This application represents the U.S. national stage under 35 U.S.C. § 371 of International Patent Application PCT/US00/15243, filed June 2, 2000, which claims priority to U.S. provisional application Serial No. 60/137,470, filed June 4, 1999.

The inventors include Shuo Chen, who was added as an inventor during the PCT phase to correct an inadvertent error in filing. The inventors are thus Roy, Lavrovsky, Tyagi, Song, Chatterjee and Chen.

As the text of the International Application was filed with the U.S. receiving office, an additional copy is not required to satisfy 35 U.S.C. § 371(c)(2). The PCT application underwent Chapter II examination, using the U.S. Patent and Trademark Office ("Office") as the

International Searching and Examination Authority (ISA/IEA). The International Preliminary Examination Report (IPER) found all claims to be drawn to a unified inventive concept, and was completely positive on all aspects of patentability for all claims.

Priority to the earlier provisional application was already properly claimed at page 1 of the specification. As a precaution, a further amendment is being made to page 1 of the specification to positively recite that this application is a nationalization of PCT Application Serial No. PCT/US00/15243.

The specification of the PCT application was amended during Chapter II examination, and the minor amendments submitted herein are made using the amended PCT specification as the starting point.

II. National Stage Claims

After according a U.S. filing date, and before calculating the filing fee, entry of the foregoing claim amendments is respectfully requested.

The changes to the claims are being made to better organize the claims, to remove certain redundant claims and to reflect certain currently preferred embodiments. The submission of new claims does not represent abandonment of any of the subject matter of the claims in the PCT application, particularly as the IPER found that the claims defined a unified invention and that all claims satisfied the requirements for patentability. The present claims are fully supported by the specification and claims of the PCT and priority application and do not in any way constitute new matter.

III. Status of the Claims

Prior to entry into the national stage, claims 1-22 were pending. These claims were examined in the PCT phase and found to have unity of invention and to comply with all requirements for patentability. Presently, claims 1-22 have been cancelled, entirely without prejudice or disclaimer. Claims 23-50 have been added, which are fully supported by the specification and unified with examined claims 1-22. The new claims are being submitted for simplicity, and to streamline examination by better organizing the claims, removing redundancies and to reflect certain currently preferred embodiments.

Claims 23-50 are therefore in the case. In accordance with 37 C.F.R. § 1.121, and for the convenience of the Examiner, a clean copy of the pending claims is included herewith as **Exhibit A**. As there have been no changes to previous claims, only additions, another claim exhibit is not necessary.

IV. Support for the Claims

Aside from focusing on certain currently preferred ribozymes, the main revisions to the claims are to better group the independent and dependent claims together and to remove redundancies from the claims. Certain dependent claims are also being added, which are fully supported by the specification. Therefore, although the claims from the PCT application have been replaced with a more organized version, the patentability in the IPER is still applicable. Particular support the present claims exists in the specification as follows.

Claim 23 is directed to a ribozyme that cleaves estrogen receptor mRNA, as supported by the original ribozyme composition claims, wherein the ribozyme comprises the sequence of SEQ ID NO:7 (RZ1) or SEQ ID NO:11 (RZ2). RZ1 and RZ2 reflect two of the preferred ribozymes,

included within original claims 2, 3, 5, 16 and 20, and as detailed in FIG. 1B and FIG. 1C. Although the sequences themselves have been present since filing, the particular SEQ ID NOs were added via amendment during the PCT phase. Support thus exists throughout the original claims and specification, in FIG. 1 and in the figure legend at page 10, as amended.

Dependent claims 24 through 27 separately recite RZ1 and RZ2, in terms of sequences that comprise and have the particular SEQ ID NOs.

Claim 28 defines that the ribozyme is formulated in a liposome, as supported by original claim 13.

Independent claim 29 is directed to a nucleic acid that encodes a ribozyme in accordance with present claim 23, as supported by original claim 10. Dependent claims 30 and 31 again separately recite RZ1 and RZ2.

Claim 32 further defines that the nucleic acid comprises a promoter, as described in the specification at page 6, first paragraph, and shown in the working examples.

Claim 33 further defines the nucleic acid as being comprised within a recombinant vector, as supported by the specification at page 3, line 24; page 4, line 19; in the text bridging pages 5 and 6; in the working examples; and as included within original claims 10, 12 and 13. The viral, adenoviral, adeno-associated viral and retroviral vectors of claims 33 and 34 are also supported by the text in the specification bridging pages 5 and 6, and by claims 12 and 13.

Claim 36 is an independent claim defining an expression vector, as supported by the specification at page 3, line 24; page 4, line 19; in the text bridging pages 5 and 6; and by original claims 10, 12 and 13. Dependent claims 37 and 38 separately recite RZ1 and RZ2.

The embodiment wherein the vector provides 5' capping and polyadenylation of the expressed ribozyme, as recited in claim 39, is supported by the specification at page 5, lines 21-23.

Claim 40 is directed to a method for reducing estrogen receptor activity by providing an effective amount of a ribozyme in accordance with present claim 23 to estrogen receptor-containing cultured cells. This is supported by the original method claims, as supplemented by the specification at least at pages 3 and 4, such as at page 3, lines 6-10 and at page 4, lines 24-25, at page 11, line 17, and in the working examples.

Claims 41 and 42 are dependent and independent claims, respectively, which refer to the inhibition of the estrogen-dependent proliferation in the cells, as supported by original claim 8 and claims dependent therefrom. Dependent claims 43 and 44 separately recite RZ1 and RZ2.

Dependent method claims 45, 46 and 47 separately recite particular forms of administration, as recited in original claim 13 (liposome), claim 10 (vector) and in claims 12 and 13 (types of vectors).

Claims 48 and 49 define the estrogen receptor-containing cells as estrogen-dependent tumor cells and estrogen-dependent breast cancer cells, as supported by original claims 8 and 9, respectively.

Finally, claim 50 specifies that an antiestrogen compound is further administered to the cells, as described in the specification, *e.g.*, at least at page 4, lines 22-25.

It will therefore be understood that no new matter is encompassed by any of the amended or newly presented claims.

V. Support for the Specification

Certain amendments are also being introduced into the specification to correct minor informalities. The amendments to the specification comply with 37 C.F.R. § 1.121, as the required instructions, text in clean form, and separate copies marked to show the changes using brackets and underlining are all submitted (**Exhibit B**). The amendments are all supported by the specification, as follows.

At page 3, reference to SEQ ID NO:1 has been deleted, as SEQ ID NO:1 does not relate to the ribozyme characteristic regions defined by nucleotide sequences, but to a routine primer (see page 13, line 17). The ribozyme characteristic regions defined by nucleotide sequences are described throughout the specification, sequence listing and figures. The catalytic region of a hammerhead ribozyme is SEQ ID NO:3, as shown at see page 6, FIG. 1B and FIG. 1C (note orientation of 5' to 3' and 3' to 5') and original claim 4.

At page 4, "clearing" has been replaced by "cleaving", to correct a typographical error.

At page 22, a transposition error has been corrected in reference to the site within the human estrogen receptor mRNA cleaved by the ribozyme termed RZ2, specifically, to list 889 as the cleavage site, rather than 894. This is consistent with the data in the specification, as exemplified by that described at page 16, line 23 and page 17, line 18, and particularly in FIG. 1C. Note also, change of "with the human in mRNA" to "within the human mRNA".

It will thus be understood that no new matter is included within the amendments to the specification.

VI. The Claims are Allowable

The IPER issued in the PCT application was completely positive for all aspects of all claims and thus supports a finding of patentability for the present claims, which recite two particular examples of the ribozymes originally claimed. Given that all requirements of patentability for RZ1 through RZ7 were met during examination in the PCT application, the present claims directed to RZ1 and RZ2 should clearly be patentable.

The positive IPER is compelling evidence that the present claims have utility and define with clarity a novel and non-obvious invention that is adequately supported by the specification. Applicants therefore urge that the present claims be directly progressed to allowance, and such favorable action is respectfully requested.

VII. Fees and Formalities

The national filing fee and claim fees are included herewith. The fees have been calculated after the present changes to the claims. Any omitted fees should be deducted from Williams, Morgan & Amerson Deposit Account No. 50-0786/4003.002300. Applicants are entitled to small entity status, and an executed declaration to this effect was submitted in the PCT phase. As a verified statement is no longer required, another copy is not being included.

The requirements for formal drawings were met in the PCT stage and additional formal versions are not enclosed herewith. The sequence listing requirements were also met in the PCT stage and a further computer disc, hard copy or statement is not required.

VIII. Conclusion

In conclusion, Applicants submit that, in light of the finding of the IPER, the claims define a unified invention that is in condition for allowance, and an early indication to this effect

is respectfully requested. Should the Examiner have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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